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Sent: 1/7/2021 1:58:32 PM
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Subject: Inside TSCA - Chloroprene

Peer Reviewers Doubt Suitability Of Chloroprene Model To Revise IRIS Value

January 6, 2021

Several EPA peer reviewers are urging agency officials not to use an industry model developed to help a chemical company's push to ease EPA's 2010 risk values for chloroprene, a chemical used to make rubber, with one reviewer saying model developers "ignored some of the available science and chose a simplistic approach."

"My overall opinion is that it is NOT PRUDENT for the EPA to grant the requested 137X relaxation of the risk estimate in the IRIS risk assessment, at this time, to Ramboll/Denka based on the science presented for this Review, as well as on my own evaluation of some of the related state-of-the-science relevant to this Project," Raymond S.H. Yang, an emeritus professor of toxicology and cancer biology at Colorado State University and one of EPA's peer reviewers, wrote in the Jan. 5 peer review report.

Yang was among four of nine reviewers who stated EPA should not adopt the physiologically based pharmacokinetic (PBPK) model that Denka Performance Elastomers LLC hired Ramboll Environ consultants to develop.

The company argues the model should be used to inform -- and reduce -- the strict inhalation cancer risk estimate EPA set in its Integrated Risk Information System (IRIS) assessment, resulting in a recommended level to protect against lung cancer of 0.2 micrograms per cubic meter of air (ug/m3).

That risk estimate, combined with EPA's modeled National Air Toxics Assessment (NATA), led to controversy and concerns among EPA and Louisiana regulators over high predicted cancer risk in the vicinity of Denka's LaPlace, LA, chloroprene plant, and efforts to reduce its emissions.

Denka, however, has argued that despite significant spending on new emissions control equipment it cannot meet the standard set in the IRIS assessment. The company challenged the agency's IRIS assessment through a request for correction (RFC) under the Data Quality Act (DQA). EPA denied the request in January 2018, based on a systematic review that IRIS staff conducted, which concluded that no information published to that point materially changed the outcome of the IRIS assessment.

But after Denka in July 2018 submitted a request for reconsideration (RFR) of EPA's denial, top EPA risk assessors reached an agreement with the company's consultants to analyze and potentially advance to peer review a new PBPK model that could be used to revise the 2010 assessment.

Such models are generally used to project absorption, distribution, metabolism and excretion (ADME) of synthetic or natural chemical substances in humans and animal species and to compare species' internal doses in risk analyses. The agreement followed a July 2018 meeting between IRIS leaders, Denka's consultants at Ramboll, and Louisiana Department of Environmental Quality (LDEQ) officials.

EPA asked Versar, a contractor, to manage the peer review, meaning that while the nine experts Versar selected met last October to discuss EPA's charge questions, they did not produce a consensus report.

Instead, the report reflects each reviewer's comments, based on their own review of the model and the discussion with the other experts at the meeting. But with four of the nine recommending against incorporating the model in the IRIS assessment, it seems unlikely EPA would do so, particularly after the agency's initial denial of Denka's RFC was based on a systematic review IRIS conducted to explore whether research on chloroprene published since the 2010 IRIS assessment would alter its conclusions.

'Left Many Holes'

EPA last summer released the model for public comment and released an internal, draft July 2020 report from a trio of scientists with EPA's IRIS program outlining the model's history and explaining IRIS scientists' goals for the peer review.

"The Ramboll (2020) model, which was developed specifically for the estimation of internal doses associated with the most sensitive endpoint observed in rodents from inhalation exposure, lung tumors, has been submitted to the EPA as significant new science to be considered to determine whether an update to the 2010 IRIS Toxicological Review of Chloroprene is warranted," EPA's report states. "The focus and ultimate objective of this peer review is to assist in EPA's determination of whether the model is of sufficient scientific quality and reliability to support consideration in an IRIS human health assessment."

The report explains that EPA "has not conducted a full quality assurance review of the current model version nor formally evaluated its suitability for use in updating the 2010 IRIS assessment" and notes that while the model was published last year in the journal *Inhalation Toxicology*, "such journal review and publication are not considered sufficient evidence of model quality and applicability for use in an IRIS assessment."

Yang and the three other reviewers suggest it is not -- while the five other panelists either supported using the model or did not appear to address that ultimate question.

"My general impression was that Ramboll/Denka had dismissed or ignored some of the available science and chose a simplistic approach of relying on a previously successful example (Revision of Methylene Chloride Risk Assessment) by the same lead scientists," Yang adds.

"In doing so for this highly reactive chemical, chloroprene, the Ramboll/Denka petition left many holes in their scientific arguments. Thus, while PBPK Modeling is a very useful tool for risk assessment, the Ramboll/Denka application is not scientifically strong enough, at this time, to support their petition."

Yang was joined in his concerns by reviewers Jeff Heys, head of Montana State University's chemical and biological engineering department; Jochem Louisse, a PBPK modeling expert with the Dutch Wageningen Food Safety Research; and Ken Portier, a biostatistician retired from the American Cancer Society and former chairman of EPA's Science Advisory Committee on Chemicals.

"Even though I see potential in the approach presented in the report, my second impression of the report is that it is simply inadequate at this time," writes Heys. "The quality and comprehensiveness of the data presented in the report is limited. Almost 20 years have passed since most of the data were collected, and there are still gaps where data is needed to better understand metabolism in the human lung, mass transfer, and more. The model itself has gaps, the report includes examples where the data contradicts model assumptions, and large uncertainty exists with some parameters."

Louisse writes, "the presented PBPK model should not be used as such to extrapolate the mouse data to a human effect dose for application in the risk assessment," before describing a series of improvements he believes are needed before the model could be used.

"As with all mathematical models that attempt to describe quite complex biochemical and toxicological processes in rodents and humans, there are issues with this model that limit its current full utilization as a tool for incorporation of in vitro test findings to predictions of in vivo processes, all in support of ongoing chemical risk assessments," writes Portier. "While not fully ready for use today, it is clear the with some additional and moderate efforts, this model, or one derived from it, will play a strong supporting role in future chemical risk assessments."

Portier's conclusion is not surprising, as he said at the close of the peer review meeting the model "may not be quite ready for prime time." -- *Maria Hegstad* (mhegstad@iwpnews.com)

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